UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

09/002,413

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/002,413	12/31/97	ALLEN, R	8661-010-999

HM12/0510

KAREN ZACHOW
MORRISON & FOERSTER, LLP
755 PAGE MILL ROAD
PALO ALTO CA 94304-1018

EXAMINER	
WILSON, M	

ART UNIT	PAPER NUMBER
1633	19

DATE MAILED: 05/10/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/002,413	Allen et al.
Examiner	**Group Art Unit**
Wilson, Michael C.	1633

☒ Responsive to communication(s) filed on *Apr 4, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *3-16, 18, 19, and 21-23* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *3-16, 18, 19, and 21-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

The request filed on 4-4-00, paper number 18, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/002413 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 11, 12, 27 and 28 have been canceled. Claims 30-32 have been added. Claims 3-10, 13-16, 18, 19, 21-26 and 29-32 are pending. Claim 24 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 3-10, 13-16, 18, 19, 21-23, 25, 26 and 29-32 are under consideration in the instant application as they relate to a method of administering cells to create an immunologically privileged site as originally elected.

Applicant's arguments filed 4-4-00, paper number 18, have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

1. Claims 4, 13, 19, 25, 29, 30 and 32 are objected to because of the following informalities: the term "consists" should be replaced with the phrase "is selected from the group consisting of"

to recite proper Markush language. Additionally, the "or" on line 4 should be changed to an "and". Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. Claims 3-16, 18, 19, 21-23, 25-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transplanting retinal pigmented epithelial cells (RPE) and non-RPE using methods known in the art, does not reasonably provide enablement for administering RPE or RPE with non-RPE to obtain any therapeutic effect using any therapeutic protein/biologically active molecule in any disease as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants state that the inventive concept of the instant invention is the discovery that RPE secrete FasL which is immunosuppressive (page 7, line 10) and that such cells can be used to make an immunologically privileged site in a mammal (page 4, line 1). The state of the art at the time of filing was such that RPE were known to provide an immune privileged site and that RPE could be transplanted to the retina to obtain a therapeutic effect or to the brain to treat Parkinson's disease (Ye et al., 1993, Current Eye research, Vol. 12, pages 629-639, see page 629, column 1, line 1; page 630, column 2, line 24; last line of abstract and page 631, column 2, line 20; Cherksey, U.S. Patent 5,618,531, April 8, 1997, see the claims, especially claim 13; column 8, line 40; column 17, line 27; column 18, lines 25-44 and column 19, line 24). Goldstein et al. teach

administering neural cells such as RPE transfected with a vector encoding tyrosine hydroxylase to the brain to treat symptoms associated with Parkinson's disease (column 4, line 50; column 17, line 49; column 15, lines 27-60). It was also known that RPE may be co-administered with other cells (Goldstein et al., column 15, line 55; Cherksey, column 9, line 2) or encapsulated to prevent rejection (Goldstein et al., column 17, line 67).

In addition, various cells were able to be transplanted to produce therapeutic molecules. For example, Sigalla et al. (Sept. 1, 1997, Human Gene Therapy, Vol. 8, pages 1625-1634) teach administering transfected pancreatic islet cells to the renal capsule and obtaining insulin release to therapeutic levels (page 1626, column 2, 2nd and 3rd paragraphs; page 1628, column 1, 4th paragraph and column 2, 4th and 5th full paragraphs). Weber et al. (1997, J. Surg. Res., Vol. 69, pages 23-32) teach administering transfected pancreatic islet cells to the renal capsule and obtaining insulin release to therapeutic levels (page 25, column 1, "Islet transplantation"; page 27, paragraph bridging columns 1 and 2). Methods of encapsulating cells, such as Langerhans cells, to obtain an immunologically privileged site were well known in the art and were used to prevent rejection of transplanted cells (for example, Fraser et al., 1995, Cell Transplantation, Vol. 4, pages 529-534).

Therefore, the state of the art at the time of filing was such that RPE could be used to create an immunologically privileged site, that specific cells secreting specific therapeutic proteins could be used to treat specific diseases.

The specification contemplates treating a number of diseases (page 1, line 23; page 3, line 26; page 5, line 31), suggests genetically engineering RPE to produce any of a number of therapeutic proteins (page 8, line 31), and suggests delivering the RPE to any of a number of tissues (page 15, line 7). The specification also contemplates co-administration of RPE with cells supplying therapeutic molecules (page 4, line 20). Co-administration can be as a single composition or as separate compositions (page 4, line 23). Co-administration as defined in the specification encompasses administering RPE cells alone because RPE "supply therapeutic molecules" such as dopamine and because the definition does not require that the cells that "supply therapeutic molecules" are non-RPE. Cells that can be co-administered with RPE are neural cells, endocrine cells, muscle cells and other cells that produce a functionally active therapeutic molecule (sentence bridging pages 6 and 7). The specification demonstrates isolating and culturing fetal RPE *in vitro* (pages 16-20) obtaining FasL expression by RPE and apoptosis of thymocytes contacted with the RPE *in vitro* (pages 21-27). The specification does not provide any guidance or examples regarding administration of cells *in vivo*. Specifically, the specification does not provide any guidance on how to use pancreatic islet of Langerhans cells (claim 22). Therefore, the skill artisan is required to rely on what was known in the art regarding how to use cells to treat disease (claims 3-10, 13-15, 25, 26 and 30-32), as pharmaceutical compositions (16, 18, 19, 29) or to produce a therapeutic protein (3-10, 13-16, 18, 19, 21-26 and 29-32).

Overall, the specification does not enable using any cell or combination of cells expressing any therapeutic molecule to treat any disease as broadly claimed. The specification and the

knowledge in the art does not teach a reasonable representative number of embodiments of the claim to enable the breadth of the claims as written. For example, Langerhans cells (claim 22) can be used to treat diabetes upon transplantation and adequate secretion of insulin. The specification and the art do not support using Langerhans cells to treat any other disease or to secrete any other therapeutic molecule. It would require one of skill undue experimentation to determine any other method of using Langerhans cells other than to secrete insulin and ameliorate diabetes.

Specifically, the specification does not enable administering Langerhans cells (claim 22) or any other cells produce growth factors, cytokines, hormones, peptide fragments of hormones, inhibitors of cytokines, differentiation factors, neurotransmitters (claims 4 and 19), interleukins, chemokines, interferons, colony stimulating factors or angiogenic factors (claims 25 and 29) to treat a neurological (claim 30), cardiac, endocrine, hepatic, pulmonary, metabolic or immunological diseases (claim 13) as broadly claimed. Given the state of the art taken with the guidance provided in the specification, it would require one of skill undue experimentation to determine the parameters required to enable the numerous therapeutic embodiments of the claims other those specific methods that were known in the art at the time of filing. This rejection is based on how to use the methods or products claimed to treat disease.

The specification does not enable encoding biologically active molecules using a nucleic acid as broadly claimed (claim 5). Biologically active molecules such as aspirin are not proteins and cannot be encoded by nucleic acids. Therefore, such non-protein biologically active molecules are not enabled.

3. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not provide a written description of how to use a kit comprising pancreatic islet of Langerhans cells and RPE cells. While applicants may have been in possession of pancreatic islet of Langerhans cells and RPE cells in containers, the specification does not provide any written description regarding how to use such a kit.

4. Claims 3-7, 9-16 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is indefinite because it is unclear whether applicants intend to administer RPE alone or RPE and non-RPE. The definition of co-administering is administration of RPE with cells supplying therapeutic molecules (page 4, line 20). It is unclear whether the definition intends to encompass administering RPE alone because RPE "supply therapeutic molecules" such as dopamine and because the definition does not require that the second cell population that "supply therapeutic molecules" are non-RPE. If two types of cells are being administered, it is unclear whether the cells are administered simultaneously. The specification states co-administration can be as a single composition or as separate compositions (page 4, line 23). It is unclear whether this is intended to mean administering two types of cells at the same time or at different times.

Claims 3, 5, 6, 15, 31 is indefinite because the phrase "said co-administered second cells" lacks antecedent basis.

Claim 5 is indefinite because the phrase a nucleic acid encoding said therapeutic protein or other biologically active molecule" is unclear. Some biologically active molecules such as aspirin cannot be encoded by a nucleic acid. It is unclear whether applicants intend to claim embodiments of encoding non-protein biologically active molecules using nucleic acids.

Claim 7 is indefinite because the phrase "said second cells that produce said biological factor" lacks antecedent basis. Claim 7 is also indefinite because the term "administering" lacks antecedent basis in claim 3. It is also unclear how the "administering" in claim 7 correlates to various "co-administering" step and the "administered" RPE and "second cells" in claim 3. The cells and method of administering the cells are unclear.

Claim 13 remains indefinite because the claim recites a disease consisting of a neurological, ...immunological disease. The claim is indefinite because the term "consists" indicates closed language; however, such language is confusing regarding a disease. How does a disease consist of a neurological disease or any of the other diseases listed? Proper Markush language is suggested, i.e. "wherein the disease is selected from the group consisting of..."

Applicants argument regarding the inclusion of overlapping elements in a Markush group is persuasive. However, the phrases "growth factor, cytokine, ... neurotransmitter" (claims 4, 19 and 32) and "interleukin, chemokine... angiogenic factor" (claim 25) remain indefinite because the group does not share a common genus. Growth factors, inhibitors of cytokines, differentiation

factors and neurotransmitters may not be proteins while cytokines and hormones are proteins (claims 4, 19 and 32). Similarly, angiogenic factors and colony stimulating factors may not be proteins while interleukins, chemokines and interferons are proteins (claim 25). The skilled artisan would not be able to determine whether they were infringing on the claimed invention because of the overlap between proteins, protein fragments and non-protein factors which do not share similar structures. In addition, the terms "growth factor," "angiogenic factor," and "differentiation factor" are indefinite because the specification is not defined in the specification and may have divergent meanings in the art. It is unclear whether applicants intend to claim factors that cause growth, angiogenesis, cell division or differentiation or merely elements that are involved in growth, angiogenesis, cell division or differentiation such as sunlight, media, minerals, amino acids, or some other factors. It is unclear what applicants consider the common genus of the elements of the Markush groups.

Claim Rejections - 35 USC § 102

5. Claims 3, 4, 7, 9, 13, 16, 19, 25 and 29 remain rejected and claims 30 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Ye et al. (1993, Current Eye research, Vol. 12, pages 629-639) for reasons of record set forth in the office action of 4-13-99, paper number 7.

Ye et al. teach treating retinal degeneration by administering $2.1x10^4$ allogeneic RPE to the retina of rabbits, obtaining immunologic privilege and an increase in the number of RPE cells in the retina (page 629, column 1, line 1; page 630, column 2, line 24; last line of abstract and

page 631, column 2, line 20). RPE cells inherently secrete FasL and cytokines as in claim 4. Applicant argues Ye et al. does not teach co-administration of RPE cells with a second cell population. Applicants argument is not persuasive. The definition of co-administration of cells as defined in the specification encompasses RPE alone because RPE secrete therapeutic proteins and because neither the definition or the claim requires that the second population be non-RPE cells. Therefore, Ye et al. anticipate all the limitations of the claims as written.

6. Claims 3, 4, 6, 7, 9, 10, 13, 16, 18, 19, 21, 23, 25, 26, and 29 remain rejected and claims 30 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Cherksey (U.S. Patent 5,618,531, April 8, 1997) for reasons of record set forth in the office action of 4-13-99, paper number 7.

Cherksey teach treating Parkinson's disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). RPE cells secrete dopamine (column 8, line 40) which is a neurotransmitter (claim 4) or chemokines (claims 4 and 19). RPE cells inherently secrete FasL and create an immunologically privileged site. Applicant argues Cherksey et al. does not teach co-administration of RPE cells with a second population of cells. Applicants argument is not persuasive. The claims recite "co-administering of RPE cells with cells ... [which] supply therapeutic protein or other biologically active molecules" which does not require that the second cells are non-RPE cells. Cherksey meets the limitation of the claims by administering RPE alone which express exogenous proteins.

In addition, Cherksey teaches administering co-cultured cells supported on a matrix to a mammal (column 9, line 2). Therefore, Cherksey anticipates claims 3-10, 13-15, 25, 26 and 30 by teaching administering RPE co-cultured with glial cells. Therefore, Cherksey anticipates a composition comprising RPE and glial cells. Applicants argue the cells of Cherksey are not allogeneic to the mammal. Applicants argument is not persuasive. Cherksey specifically states allogeneic cells can be used for administration to a mammal (column 11, line 37).

Claim Rejections - 35 USC § 103

7. Claims 3, 14 and 15 remain rejected and claims 16, 18, 19, 21, 23, 29, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997).

Cherksey teach treating symptoms of Parkinson's disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). It would have been obvious to one of ordinary skill in the art to re-administer cells (claims 14 and 15) using the teachings of Cherksey et al. to sustain the therapeutic effects. It was common practice for the ordinary artisan to repeat treatments to obtain therapeutic effects at the time of filing. Claims 16, 18, 19, 21, 23, 29 and 32 require that the RPE are allogeneic to a second cell population which is not required of claims 3, 14 and 15. While Cherksey does not teach that the co-culture of cells is allogeneic, Cherksey teaches that the cells

of the instant invention may be allogeneic to the host (column 11, line 37). Thus, it would have been obvious to one of ordinary skill at the time the invention was made to combine allogeneic glial cells and RPE to transplant the cells as suggested by Cherksey (column 9, line 2).

8. Claims 3, 5 and 8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) in view of Goldstein et al. (U.S. Patent 5,300,436, April 5, 1994) for reasons of record set forth in the office action of 4-13-99, paper number 7.

Cherksey teach treating symptoms of Parkinson's disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). RPE and glial cells inherently supply therapeutic proteins such as neurotransmitters. Cherksey does not teach transfecting cells with nucleic acids encoding a protein. However, Goldstein et al. teach administering cells transfected with a vector encoding tyrosine hydroxylase to the brain to treat symptoms associated with Parkinson's disease (column 4, line 50; column 17, line 49). Thus, it would have been obvious to one of ordinary skill in the art to combine the method of administering RPE taught by Cherksey with the cells transfected with tyrosine hydroxylase as taught by Goldstein et al. Motivation is provided by Goldstein et al. by stating the RPE cells can be transfected with tyrosine hydroxylase (column 15, lines 26-61, see line 59).

Applicants argue the reference do not teach co-administration of two different cell types which are allogeneic to the animal. Applicants argument is not persuasive because the claims do not require administration of RPE and non-RPE. However, Cherksey clearly states that the cells may be combined with glial cells for readministration into an allogeneic host (column 9, line 2; column 11, line 37).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson

Karen M. Hauda

Karen M. Hauda
Patent Examiner